

Candida and Oral Candidosis: A Review

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ABSTRACT: *Candida* species are the most common fungal pathogens isolated from the oral cavity. Their oral existence both as a commensal and an opportunist pathogen has intrigued clinicians and scientists for many decades, and recent investigations have revealed many attributes of this fungus contributing to its pathogenicity. In addition, the advent of the human immunodeficiency virus infection and AIDS has resulted in a resurgence of oral *Candida* infections. Clinicians are witnessing not only classic forms of the diseases but also newer clinical variants such as erythematous candidosis, rarely described hitherto. Therefore, this review is an attempt at detailing the current knowledge on *Candida* and oral candidoses together with the newer therapeutic regimes employed in treating these mycoses.

KEY WORDS: *Candida*, oral candidosis.

I. INTRODUCTION

The advent of the human immunodeficiency virus infection and AIDS has resulted in a resurgence of oral *Candida* infections that are usually seen in the very young, the very old, and the very sick. *Candida albicans* is the most common *Candida* species isolated from the oral cavity both in health and disease, while other species such as *C. glabrata*, *C. tropicalis*, and *C. guilliermondii* are infrequently but consistently isolated (Samaranayake, 1990a). *C. albicans* is a dimorphic fungus existing both in the blastospore phase (syn. yeast phase, blastoconidial phase) and the hyphal or mycelial phase. Although these organisms typically colonize mucocutaneous surfaces, the latter can be portals of entry into deeper tissues when host defenses are compromised (Rogers and Balish, 1980).

An excellent account of systemic candidosis can be found in monographs by Odds (1988) and Tumbay *et al.* (1991), while the subject of oral

candidosis has been addressed recently in detail by Samaranayake and MacFarlane (1990).

II. TAXONOMY AND TYPING OF CANDIDA

The genus *Candida* is a collection of some 150 asporogenous yeast species. Because of their inability to form a sexual stage, they are most often classified among the fungi imperfecti in the class Deuteromycetes (Lodder, 1970). Seven *Candida* species are of major medical importance, and of these *C. albicans*, *C. tropicalis*, and *C. glabrata* are the most frequently isolated (more than 80%) from medical specimens. The other pathogenic *Candida* species are *C. parapsilosis*, *C. stellatoidea*, *C. guilliermondii*, *C. krusei*, and *C. pseudotropicalis*. *Candida stellatoidea* is differentiated from *Candida albicans* by its inability to assimilate sucrose. However, the high DNA homology between the two yeasts led Meyer *et al.*

(1984) to classify *C. stellatoidea* as a sucrose-negative variant of *C. albicans*.

Within the class Deuteromycetes, the distinguishing feature of the *Candida* species is their ability to form pseudohyphae, the only exception being *C. glabrata* (Lodder, 1970). A number of techniques have been used over the years to differentiate *Candida* isolates either belonging to different species or belonging to the same species. These are annotated below.

A. DNA Base Composition

The base composition of nuclear and mitochondrial DNA in yeasts is expressed as the molar percentages of guanine plus cytosine (G+C) (Kurtzman and Phaff, 1987). The G+C content among species within a genus often varies within 10%, but differences much above 10% may suggest that the genus in which the organisms have been placed is composed of several genera (Olsen, 1990).

B. Typing and Mapping of DNA

DNA typing methods based on digestion and electrophoresis of DNA fragments appear to offer important potential advantages over phenotypic methods in taxonomy. Such methods provide a basis for the development of cloned probes for studies on DNA homology (Scherer and Stevens, 1987; Fox et al., 1989).

C. DNA-DNA Homology

DNA-DNA complementarity experiments measure the fidelity of complementary base pairing of denatured DNA strands from test pairs (Leth and Stenderup, 1969).

D. Ribosomal RNA

Ribosomal RNA (rRNA)-DNA homology studies have been made with species of relatively few genera. The data suggest that intragenetic relationships established with this method are not usually meaningful, owing to the high degree of conservation of the DNA sequences coding for rRNA (Phaff, 1984).

E. Enzymes

The amino acid sequence of enzymes such as glutamine synthetase and superoxide dismutase determined with quantitative microcomplement fixation may help evaluate the relationship between yeasts (Kurtzman and Phaff, 1987). Alloenzyme electrophoresis is based on the idea that genetic diversity develops over time. This implies that genetically distant organisms show major differences in protein composition, and that more closely related organisms show a high degree of similarity in protein composition. Alloenzyme analysis is even more sensitive for studying intraspecific variation among yeasts than DNA-DNA sequence complementarity (Kurtzman and Phaff, 1987; Odds, 1988).

F. Cellular Protein/polypeptide Profiles

Autoradiographic analysis of (³⁵S) methionine-labeled cellular proteins separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis shows that different *Candida* species and other yeast species produce distinct patterns (Shen et al., 1988).

G. Killer Systems

Killer toxins of yeast may be useful for differentiating strain types among the pathogenic species for surveillance studies (Morace et al., 1983) and to determine their geographic distribution (Young, 1987).

H. Carbohydrates

Capsular and cell wall polysaccharides have been used in taxonomic studies, particularly at the generic level (Weijman and Rodriguez De Miranda, 1988). Differentiation between yeasts has also been made from the absence or presence of glucuronic acid or D-xylose in the cell walls (Phaff, 1984).

I. Other Typing Methods

Other typing methods that use less sophisticated technology and commercially available media include resistogram method, API ZYM,

API 20C, and boric acid resistance assay, and colony morphotyping (Silverman *et al.*, 1990).

III. *CANDIDA* CARRIAGE IN THE ORAL CAVITY

A. Prevalence Data

Symptom-free oral carriage of *Candida* organisms has been recognized for many years. Figures obtained on the frequency of yeast carriage in the oral cavity are dependent on isolation techniques and time of sampling (Odds, 1988).

The reported prevalence in clinically normal mouths of healthy adults ranges from 3 to 48% (Arendorf and Walker, 1980), and in 45 to 65% of healthy children (Odds, 1988).

Odds (1988) has analyzed a large number of papers on oral carriage from the literature (Table 1). From 32 papers on yeast isolation from the oral cavity in "normals", the median carriage frequency was 34.4% for all yeasts and 17% for *C. albicans* alone. In children there was a peak in carriage between the age of 1 week and 18 months. *C. albicans* is the most dominant species, followed by *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, and *C. krusei*. Other *Candida* species and genera

TABLE 1
Carriage of Oral Candida

Sample details	No. of papers	Range	Published carriage frequencies (%)		
			Weighted mean ^a	Simple mean ^b	Median
Yeast isolations — "normals"					
Oral/pharyngeal swab	20	2.0–69.1	16.9	24.8	27.7
Saliva/mouthwash	10	25.0–71.3	41.1	40.5	36.8
Imprint culture	3	39.4–50.0	46.8	44.6	44.4
Overall ^c	32	2.0–71.3	25.5	31.5	34.4
Yeast isolations — patients					
Oral/pharyngeal swab	23	12.7–76.2	42.1	45.3	48.3
Saliva/mouthwash	9	35.0–75.0	52.3	56.2	55.4
Imprint culture	2	34.0–66.0	—	—	—
Overall ^c	34	12.7–76.2	47.0	50.2	54.7
<i>C. albicans</i> isolation — "normals"					
Oral/pharyngeal swab	16	1.9–41.4	16.3	17.9	17.6
Saliva/mouthwash	5	4.3–62.3	29.5	24.2	23.1
Overall ^c	20	1.9–62.3	17.7	19.4	17.0
<i>C. albicans</i> isolations — patients					
Oral/pharyngeal swab	21	6.0–69.6	35.9	36.8	36.6
Saliva/mouthwash	6	15.4–42.0	33.5	33.5	36.3
Imprint culture	2	43.4–60.0	—	—	—
Overall ^c	32	6.0–69.6	40.6	37.5	38.1
Yeast carriage at different ages ^d					
Neonates up to 7 d	5	7.1–31.7	16.3	17.3	16.0
Infants aged 1 week–18 months	3	40.6–54.2	44.1	46.3	44.0
Children >18 months	3	3.4–36.0	8.7	15.1	6.0
Adults	8	2.0–69.1	20.3	25.1	24.5

^a Weighted by number of cases in study.

^b That is, arithmetic mean of frequencies quoted.

^c Including "not stated", etc.

^d Based on swab samples only to minimize bias because of sampling method.

From Odds, F. C.: *Candida and Candidosis: A Review and Bibliography*, 2nd ed., Balliere Tindall, London (1988).

(*Rhodotorula*, *Saccharomyces*, etc.) are rare and transient (Stenderup, 1990).

B. Factors Affecting *Candida* Carriage

Carriage is more frequent in females than males, and during the summer months (Barlow and Chattaway, 1969). The similarities between carriers and noncarriers of *C. albicans* with respect to age, caries experience, periodontal status, and intraoral temperature indicate that many factors do not significantly influence candidal carriage (Arendorf and Walker, 1979). Some factors that do influence carriage, however include:

1. Salivary Factors

The quality and the quantity of saliva and its constituents play a critical role in modulating yeast cell populations in the oral cavity. Lack of salivary flushing action and the absence of antifungal salivary constituents such as lactoferrin and lysozyme may help explain the increased oral yeast carriage and infection seen in xerostomic patients (MacFarlane, 1990) and in animal models (Jorge *et al.*, 1983). The correlation between *Candida* carrier status and pH on the surface of the tongue shows that the carriage of yeast is higher in acidic salivas (Arendorf and Walker, 1979).

2. Temporal Variations

Candida counts increase during sleep but are reduced by taking a meal and by toothbrushing. Generally, counts are highest early in the morning, and, furthermore, where counts are low, the organisms cannot be isolated except in the early morning. The early morning saliva sample is also the most dependable for making a comparison of the *Candida* population within and between individuals (MacFarlane, 1990).

Despite the above observations, early morning saliva specimens from edentulous subjects not wearing dentures are consistently low in *C. albicans*. This has been attributed to sleeping without dentures and the consequent alteration in the oral environment. Davenport (1970) has found

larger numbers of *Candida* in smears from dentures than from mucosa. When dentures are worn at night, the early morning saliva *Candida* count is high; when dentures are not worn at night, the early morning count is the lowest. The increased *Candida* count following reinsertion of the dentures suggests that plaque on the dentures harbors *C. albicans* (Budtz-Jorgensen, 1990).

The increase in both the frequency of carriage and the density of candidal colonization in denture wearers compared with dentate subjects suggests that prostheses encourage the presence and growth of candidal species (Arendorf and Walker, 1979).

3. Smoking

Some studies have suggested that smoking does not affect *Candida* carriage significantly (Bastiaan and Reade, 1982; Oliver and Shillitoe, 1984), while others have reported that smoking significantly increased carriage by 30 to 70% (Arendorf and Walker, 1980).

It has been suggested that cigarette smoking might lead to localized epithelial alterations that allow colonization by *Candida* (Arendorf and Walker, 1980). An alternative hypothesis is that cigarette smoke provides nutrition for *C. albicans*. The related species of *C. tropicalis*, *C. guilliermondii*, and *C. pulcherrima* have inducible enzyme systems that would allow them to replicate using polycyclic aromatic hydrocarbons as their source of carbon and energy (Takagi *et al.*, 1980). This relationship between cigarette smoke and *Candida* is particularly important, as the enzyme system in question can increase the carcinogenic activity of the hydrocarbon and candidal leukoplakia might have a higher potential for malignant changes than other leukoplakias (Cawson and Binnie, 1980, also see below).

4. Oral Topography

C. albicans colonizes mainly the posterior dorsum of the tongue (Arendorf and Walker, 1980, Oliver and Shillitoe, 1984). It may be relevant that this is the site at which median rhomboid glossitis occurs, a condition that is usually, if not always, associated with proliferation of candidal

hyphae (Walker and Arendorf, 1990). In denture wearers, the fitting surface of the denture is the main reservoir of the yeasts (Budtz-Jorgensen, 1990).

5. Immune Status

Carriage of *Candida* has been shown to be greater in persons of blood group O and nonsecretors of blood group antigens in saliva (Mason *et al.*, 1988) possibly mediated by an effect on *C. albicans* adhesion to epithelia (Blackwell *et al.*, 1986). Specific antibodies to *C. albicans* (Vudhichamnong *et al.*, 1982) and decreasing T-lymphocyte helper-to-suppressor ratios (Melbye *et al.*, 1985) may also influence carriage.

6. Oral Microflora

A number of studies have indicated that *Candida* can be isolated from the oral cavity with greater prevalence and in greater numbers during tetracycline therapy (McGoven *et al.*, 1953). Animal studies have shown that suppression of the commensal oral flora by diets containing broad spectrum antimicrobials (e.g., tetracyclines) are a prerequisite to initiate and establish oral infection (Fisker *et al.*, 1982), although other studies indicate that antibiotics are not essential for initiation of oral candidosis in murine models (Allen and Beck, 1983).

7. Candida Carriage in Hospitalized Patients

The oral carriage of yeasts is higher in hospitalized than ambulant patients (Table 1), with a median carriage rate of 54.7% for all species and a median of 38.1% for *C. albicans* alone. *C. glabrata* is often found in significant numbers, with the highest frequency in denture wearers and those with denture-induced stomatitis (Odds, 1988). In one study of denture wearers without stomatitis, *C. glabrata* was found in 48% and *C. albicans* in 84%, with an association of the two species in 41%. High carriage frequencies (up to 78%) are also found in the hospitalized elderly (Cumming *et al.*, 1990; Wilkieson *et al.*, 1991).

Thus, a consequence of hospitalization is an increase in carrier rates, but high counts alone do not necessarily mean that the patient will have clinical symptoms of candidosis (Mitchell *et al.*, 1982).

IV. HOST ORAL DEFENSES AGAINST CANDIDA INFECTION

The host defenses against *Candida* have been reviewed recently (Greenfield, 1992). The oral epithelium acts as a physical barrier, and epithelial turnover *per se* contributes to defense.

A. Microbial Interactions

Competition and inhibition by the oral flora are also important in limiting the establishment and overgrowth of fungi (Epstein *et al.*, 1984). Microbial interactions include nutritional competition, alteration in the microenvironment, and elaboration of toxic and metabolic byproducts. The indigenous bacterial flora can decrease colonization by *C. albicans* by competing for adherence sites on epithelial cells (Samaranayake, 1990).

In contrast, *Candida* may also maintain synergistic relationships with pathogenic flora. Thus, synergism between *C. albicans* and *Staphylococcus aureus* has been observed (MacFarlane, 1990). Noteworthy in this context is the co-infection by *Candida* spp. and *S. aureus* in angular stomatitis (Warnakulasuriya, Samaranayake, and Peiris, 1990).

Alterations in the microbial flora associated with systemic illness, hormonal changes, and use of medications (corticosteroids and antibiotics) may be significant in predisposing to candidosis (Rogers and Balish, 1980). For example, an increased prevalence of *C. albicans* in saliva has been shown in patients treated with antibiotics and corticosteroids and in diabetic patients (Knight and Fletcher, 1971).

B. Salivary Nonimmune Factors

1. Iron

Iron is an essential nutrient of both bacteria and fungi, and Weinberg (1974) noted evidence that increased susceptibility to infectious agents

was associated with elevated levels of iron in serum. In contrast, the iron-binding proteins, including lactoferrin, have been shown to inhibit growth or kill *C. albicans* (Nikawa *et al.*, 1993). Samaranayake (1986) has reviewed the role of iron in oral candidosis.

2. Lysozyme

Lysozyme (muramidase) is a low-molecular-weight protein present in relatively high concentration in the oral cavity, saliva, gingival crevicular fluid, and polymorphonuclear leukocytes (Brown *et al.*, 1975). Lysozyme can, by increasing permeability, damage *Candida*; *C. albicans* and *C. glabrata* are the least sensitive to lysozyme, whereas *C. krusei* is the most sensitive (Tobgi *et al.*, 1988).

Lysozyme has also been shown to stimulate phagocytosis in association with IgA. The hydrolytic action of lysozyme on cell wall structural proteins, injury to cytoplasmic membranes, agglutination of *Candida* species, and stimulation of phagocytosis indicate a significant role for lysozyme in host defense in oral candidosis (Hill and Porter, 1974).

3. Salivary Histidine-Rich Polypeptides

Salivary histidine-rich polypeptides (HRPs), together with antimicrobial proteins such as lysozyme, are antifungal and in healthy individuals suppress *Candida* levels (Rayhan *et al.*, 1992).

4. Lactoferrin

Lactoferrin is found in parotid and submandibular saliva and in polymorphonuclear leukocytes, and concentrations in saliva increase dramatically during inflammation of the oral mucosa and parotid gland (Tabak *et al.*, 1978). Its antifungal activity is believed to be because of binding of iron (Soukka *et al.*, 1992). Lactoferrin has also been postulated to enhance the antibacterial activity of lysozyme by attenuating the inhibitory effect of iron on this enzyme (Masson and Heremans, 1971). Furthermore, as with lysozyme, there appear to be interspecies and intraspecies variations in the sensitivity of *Candida* to lactoferrin (Nikawa *et al.*, 1993). The latter group has demonstrated that lactoferrin may con-

fer structural changes on the cell walls of *Candida* and have demonstrated bleb-like cell wall modifications in lactoferrin-treated yeasts.

5. Lactoperoxidase

The lactoperoxidase (LPO) system in the mouth possesses antimicrobial activity (Tenovuo *et al.*, 1977) involving multiple factors (H_2O_2 and halides) and modes of action, including halogenation of microbial proteins, aldehyde formation, and oxidation of lipid sulfhydryl groups (Klebanoff, 1974). Significant candidacidal activity was demonstrated when *Candida* organisms were incubated with a conjugate of lactoperoxidase, xanthine oxidase, and specific antibody against *Candida* (Okuda *et al.*, 1980).

6. Salivary Glycoproteins

Salivary glycoproteins antigenically similar to host cell surface antigens (blood group antigens) affect competition and prevent surface adherence of microbes to the mucosal surface; this results in augmentation of the cleansing action of saliva (MacFarlane, 1990; also see below).

C. Immune Factors in Host Defense Against *Candida*

1. Granulocytes

Bone marrow-derived cells, probably neutrophils, are crucial to the natural resistance to *C. albicans* (Ashman and Papadimitriou, 1990). Individual granulocytes can phagocytose up to 10 yeasts (Pereira and Hosking, 1984), but the proportion killed remains constant at about 20 to 30% regardless of the number ingested. The myeloperoxidase (MPO)-hydrogen peroxide-halide system appears to play a major role in the intracellular killing of *Candida* (Lehrer and Cline, 1969). Susceptibility to candidal and staphylococcal infection has been the chief problem resulting from MPO deficiency (Lehrer and Cline, 1969). Okuda *et al.* (1991) reported a case of alveolar pyogenic granuloma in the maxilla caused by infection with *C. albicans* in a patient with MPO deficiency.

The candidacidal activity of human neutrophils has been shown to be enhanced independently by immune interferon (IFN- α) and tumor necrosis factor (TNF) (Djeu *et al.*, 1986). In the presence of suboptimal levels of IFN- α , TNF acts synergistically to increase neutrophil effector function. Cytokines such as granulocyte colony-stimulating factor (G-CSF) can increase production of neutrophils by bone marrow and increase resistance to *C. albicans* (Matsumoto *et al.*, 1987). Granulocytes can also kill the mycelial elements of *Candida*, and the capacity to bind and to generate microbicidal oxidants is augmented by serum opsonins (Diamond, 1988).

2. Cell-Mediated Immunity

Although phagocytosis represents the prime mechanism by which *C. albicans* is controlled, the intrinsic candidacidal abilities of both granulocytes and macrophages are quite limited, and full expression of their effect is dependent on augmentation by cytokines synthesized or induced by T cells (Ashman and Papadimitriou, 1990). *Candida* infections are consistently seen when cell-mediated immunity is depressed (Valder *et al.*, 1987). Lymphokine production by T cells is initiated by an antigen-specific interaction. This process involves antigen processing and presentation by macrophages or other accessory cells that carry appropriate (compatible) class I and class 2 MHC antigens on their surface. In this context, it is significant that human *Candida*-specific T cells require HLA-DR-compatible macrophages for their activation (Jose *et al.*, 1981), and that *Candida* infection markedly increases the expression of HLA-DR and HLA-DQ antigens on the surface membranes of epithelial cells (Jontell *et al.*, 1986).

Activation of T cells produces a wide range of lymphokines that can, in turn, modulate the functions of macrophages and other leukocytes. Interferon-gamma (IFN- γ) is the only lymphokine known to increase the microbicidal activities of macrophages: it also initiates TNF synthesis by them (Papadimitriou and Ashman, 1989). In the presence of suboptimal levels of IFN- γ , *Candida* killing by neutrophils is markedly enhanced by TNF. Unfortunately, the cytokines produced as a result of T cell/macrophage interactions have the potential to exacerbate symptoms of illness as

well as enhancing clearance of the infection (Ashman and Papadimitriou, 1990).

Polysaccharide antigens of *C. albicans* may generate a complex series of interactions that suppress both T- and B-cell responses (Piccalella, Lombardi, and Morelli, 1981). These effects may eventually block the synthesis of both interleukin 2 (IL-2) and IFN- γ , as well as the expression of the Tac antigen (the IL-2 receptor) by normal T cells (Lombardi *et al.*, 1986); antigen presentation and interleukin 1 (IL-1) production by monocytes may also be affected (Lombardi *et al.*, 1985).

3. Humoral Immunity

Serum antibodies can affect the growth of *C. albicans* (Grappel and Calderone, 1976). The major specific immunologic factor in saliva is sIgA, which may be a primary defense against oral candidosis by aggregating the organisms and by preventing their adherence to mucosal epithelium (Epstein *et al.*, 1982).

Humoral- and cell-mediated immunity to *C. albicans* may comprise a second line of defense when penetration of mucosa or systemic infection occurs. Wilton and Lehner (1980) reported that both mucocutaneous and systemic candidosis are typically associated with defects in the cell-mediated immune response. These can be caused by deliberate immunosuppression (as in transplant patients) or in cancer patients treated with cytotoxic drugs; they can be associated with some underlying disease, such as the human immunodeficiency virus (HIV) infection, or they may reflect specific deficiencies in the cell-mediated immune response, as in chronic mucocutaneous candidosis (Kirkpatrick, 1988).

4. The Relationship Between *C. Albicans* And Heat Shock Protein 90

Prokaryotic and eukaryotic cells respond to the stress of sudden rise in temperature by increasing the rate of synthesis of so-called "heat shock proteins" (HSPs) (Lindquist and Craig, 1988). HSP90, together with its breakdown products, is now recognized as an immunodominant antigen in fungal infections, and seroconversion

to it is associated with recovery from systemic candidosis (Burnie and Matthews, 1991).

Sera from patients with culture-confirmed systemic candidosis contain detectable antibodies against *C. albicans*, but whereas survivors produce a major antibody response to the 47-kDa antigen of *Candida*, fatal cases produce little or no antibody (Matthews *et al.*, 1987). The 47-kDa antigen is a heat-stable breakdown product of the larger 92-kDa antigen that circulates in the sera of these patients (Matthews *et al.*, 1987). The 92-kDa antigen is a heat shock protein HSP90 (Matthews, 1992). Antibody to the 47-kDa antigen is also present in patients with chronic mucocutaneous candidosis (CMC) and in those with AIDS (Matthews, 1992; Burford-Mason, *et al.*, 1987). If the antibody to the 47-kDa antigen is protective, this would help explain the rarity with which such patients develop systemic candidosis, despite severe superficial candidal infections (Matthews, 1992). Indeed, in a neonate with *Candida* meningitis, who recovered, antibody to the 47-kDa antigen was the first antibody to appear in the cerebrospinal fluid (Burnie *et al.*, 1986).

C. albicans HSP90 shows >50% direct homology with human HSP90. Most of the antibodies produced by infected patients were directed against highly conserved epitopes shared with human HSP90. Therefore, autoreactive antibodies are produced commonly in patients recovering from systemic candidosis without any clinical evidence of autoimmune sequelae (Matthews, 1992).

Human HSP90 is essentially intracellular, whereas candidal HSP90 circulates in the plasma in large amounts (Matthews, 1992). A pathogenic effect resulting from candidal HSP90 might be the disseminated intravascular coagulation sometimes associated with systemic candidosis (Rebbe *et al.*, 1987). Antibody to HSP90 would then be protective because it neutralizes the activity of the extracellular fungal HSP90. The possible role of HSP90 in candidosis is discussed fully elsewhere (Matthews, 1992).

V. PATHOGENICITY OF *CANDIDA* SPECIES

The factors involved in the pathogenicity of *C. albicans* have been reviewed recently (Krempl-

Lamprecht, 1991). The pathogenesis of different biotypes and strains of *C. albicans* varies (Allen and Beck, 1983).

A. Enzymes of *Candida*

It has been suggested that *C. albicans* produces an "endotoxin" (Dobias, 1964), but the levels of endotoxin found *in vivo* may not be sufficient to produce toxic effects (Cutler *et al.*, 1972). Alternatively, the organisms may produce enzymes that facilitate penetration of the mucous membranes (Arendorf and Walker, 1979). *Candida* certainly has the ability to produce phospholipases and Pugh and Cawson (1977) have shown that the phospholipases are concentrated at the tips of fungal hyphae and localized in the vicinity of host cellular compartments where active invasion is occurring. These enzyme activities were found in most *C. albicans* strains but not in organisms known to be less virulent than *C. albicans* (Samaranayake *et al.*, 1984b), such as *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*.

Extracellular proteinases have also been implicated in the pathogenicity of *C. albicans* (MacDonald and Odds, 1980). Proteinase-deficient strains are noninvasive (MacDonald and Odds, 1983), and the pattern of adherence also reflects the expression of secretory proteinase (Borg and Ruchel, 1988). Salivary proteins, including IgA, can be almost completely degraded by acidic proteinases of *Candida* especially under low pH conditions (Samaranayake *et al.*, 1993). Recently, it has been shown that parotid saliva is more resistant to the proteolytic action of *Candida* proteinase when compared with mixed saliva (Samaranayake *et al.*, 1993). Acid proteinase (aspartyl proteinase) production is increased by *C. albicans* isolated from later stages of HIV infection and may contribute to candidosis. The role of alkaline proteinase in the oral cavity is not clear yet.

B. Temperature Variations

The virulence of *C. albicans* can also be influenced by the temperature at which it is grown (Hazen and Hazen, 1987). Virulence is associated with increased germ tube production by yeast

grown at the lower temperature. These, in turn, display enhanced adherence characteristics compared with the parent yeasts mainly in the blastospore phase (Tronchin *et al.*, 1988). Yeasts grown at room temperature are more resistant to killing by polymorphonuclear leukocytes (Antley and Hazen, 1988). The clinical implications of these phenomena, if any, is not known.

C. Adhesion of *Candida*

There is a vast literature on this topic, which is excellently reviewed by Kennedy (1988). A relationship has been suggested between the adherence of *C. albicans* to surfaces and its ability to colonize and cause disease (Odds, 1988). An important aspect of the pathogenicity of *C. albicans* may be its nonspecific affinity and binding to acrylic resin (*Candida*-associated denture stomatitis) and other plastics (catheter-related candidosis) (Shepherd *et al.*, 1985). The mechanism of attachment is believed to involve the interaction of cell wall components of *C. albicans* with the target surface (McCourtie and Douglas, 1984).

The initial yeast to epithelium contact may be due to nonspecific adhesion followed by specific adhesion (Sandin, 1987). Modification of both host and yeast cells have been observed once *C. albicans* is attached. It may be that the *Candida* cells "bump" into epithelial cells, initially binding reversibly and then physiological changes strengthen the adhesion. These changes could modify the epithelium to the extent that more, or different, receptors are exposed that stabilize and strengthen adhesion (Tronchin *et al.*, 1984). It has also been suggested that the adhesion of *C. albicans* to oral mucosal cells might entail interactions involving divalent cations (Kennedy, 1988). The adsorption of macromolecules onto epithelial cells is believed to occur via electrostatic interactions involving calcium ions and other ionic groups. *Candida* cells might also attach by similar mechanisms.

The extent and strength of the adhesion depends on the initial surface properties of both the organisms and substratum involved and can be influenced by several factors (Rutter, 1984). These are listed in Table 2.

The cell surface structures promoting adhesion are highly dependent on the culture condi-

TABLE 2
Factors Affecting Adhesion of Yeasts

Factors related to yeast cells

- Medium/cultivation
- Phenotype
- Germ tubes/hyphae
- Extra-cellular polymeric material (EP)
- Floccular/fibrillar surface layers
- Mannan
- Chitin
- Hydrophobicity
- Cellular lipids

Factors related to host cells

- Cell source
- Mucosal cell size and viability
- Fibronectin
- Fibrin
- Sex hormones
- Yeast carriers vs. patients with overt candidosis

Environmental factors affecting adhesion

- Cations
- pH
- Sugars
- Saliva
- Humoral antibody and serum
- Antibacterial drugs
- Bacteria
- Lectins

tions of the yeast. Optimal adhesive activity of *C. albicans* is seen only when the cells are grown in defined media at 25°C (Kennedy, 1988). It has also been observed that the phenotypic variant, "white" cells of *Candida* are significantly more adhesive to buccal epithelial cells than are "opaque" cells (Kennedy *et al.*, 1988). The adherence of the hyphal phase of *C. albicans* to cells is significantly greater than that of the blastospore phase cells (Samaranayake and MacFarlane, 1982; Tronchin *et al.*, 1988) so that conditions conducive to germ tube formation result in significantly greater adherence (Sobel *et al.*, 1981). It is not clear why viable germ tubes enhance adherence, but it has been suggested that there may be changes in surface components such as adhesins that could account for the increased adherence (Kimura and Pearsall, 1978; Tronchin *et al.*, 1988). Further, germ tubes promote clumping of yeast cells and binding of adjacent filaments, thus bringing a larger number of *Candida* organisms into contact with epithelial cells (Sobel *et al.*, 1981).

It is possible that sterols may be involved in adhesion mechanisms; the role of lipids is reviewed elsewhere (Mishra *et al.*, 1992).

The extracellular polymeric material (EP) originating from the yeast cell surface appears important in facilitating adhesion. EP originating from the cell surface of *C. albicans* contains surface glycoproteins responsible for yeast adhesion, and it is thought that the protein portion of the mannoprotein is probably more important than the carbohydrate moiety (Critchley and Douglas, 1987).

There are at least two surface types of *Candida* adhesin: floccular and fibrillar (Kennedy, 1988). Whereas the floccular layer mediates adhesion to oral mucosal epithelium, isolates that are able to synthesize a fibrillar surface layer demonstrate increased adhesion to epithelial cells (McCourtie and Douglas, 1984).

The interaction of bacteria and fungi on epithelial surfaces has aroused clinical interest for some time. The indigenous oral flora may interfere with adherence and colonization by *Candida* organisms. It has been observed that the normal resident bacterial flora suppresses fungal colonization, whereas alteration and reduction in surface bacteria, such as is seen after antibiotic therapy, are associated with fungal colonization and often symptomatic disease (Saigh *et al.*, 1978).

Adherence is temperature dependent and can occur at pH values consistent with those of the vaginal (pH 5.0) and oral mucosal surfaces (pH 7.0) (Samaranayake and MacFarlane, 1982). However, at low pH conditions, pH 3 to 4, the adherence of *Candida* to both epithelial and acrylic surfaces is significantly increased (Samaranayake *et al.*, 1980).

Secretory immunoglobulin A (sIgA) can inhibit the adherence of *C. albicans* to human oral epithelial cells (Vudhichamnong *et al.*, 1982). Chitin derivatives can inhibit the adherence of *C. albicans* to acrylic (Segal *et al.*, 1992). The effect of blood group secretor status is discussed below.

D. Switching Phenomena

C. albicans frequently exhibits variant colonial forms when grown *in vitro*. For instance, a

smooth colony-forming yeast when inoculated onto an agar surface may produce a proportion of colonies with rough surfaces (smooth to rough switching). It is known that switching can be triggered by low doses of UV radiation, and once triggered into the high-frequency switching mode *C. albicans* exhibits high rates of alterations in colony morphology (Soll, 1992). Thus, *C. albicans* has the capacity to switch frequently and reversibly between several variants, heritable, phenotypes (Soll, 1992). Switching is associated with changes in micromorphology and physiologic properties as well as a number of putative virulence traits. One switching system, "white-opaque" transition, has been examined for the capabilities of the two phenotypes to adhere to oral epithelial cells. "White" cells were shown to be significantly more adhesive than were "opaque" cells (Kennedy *et al.*, 1988), and there may be differences in hyphae and antigenic pattern (Soll, 1992).

It has been postulated that the switching mechanisms of *Candida* may help potentiate its pathogenic features (1) during invasion of different body environments, (2) by eluding the immune system by altering its surface antigenicity, and (3) by escaping the action of antifungals. (For a recent review of this phenomenon see Soll, 1992.)

VI. FACTORS PREDISPOSING TO ORAL CANDIDA INFECTIONS

The major local and systemic factors that predispose humans to candidosis have been classified by Odds (1988) as natural factors, dietary factors, mechanical factors, and iatrogenic factors. Oksala (1990), in a review of literature of the factors predisposing to oral candidal infection, listed those shown in Table 3. These are discussed below.

A. Prostheses

As far as chronic local irritants, ill-fitting appliances, and inadequate hygiene are concerned, high salivary yeast counts are much more common in full-denture wearers than in dentate subjects (Parvinen, 1984). Yeasts are demonstrable in 78 to 100% of patients with denture-induced

TABLE 3
Factors Predisposing to Oral Candidosis

Chronic local irritants
Ill-fitting appliances
Inadequate care of appliances
Disturbed oral ecology or marked changes in the oral microbial flora by antibiotics, corticosteroids, xerostomia
Dietary factors
Immunological and endocrine disorders
Malignant and chronic diseases
Severe blood dyscrasias
Radiation to the head neck
Abnormal nutrition
Age
Hospitalization
Oral epithelial dysplasia
Heavy smoking

From Odds, 1988; Kostiala, Kostiala and Kahanpaa, 1979; Petersen, 1984; Oksala, 1990.

stomatitis (Olsen, 1974). However, in microbiological studies of patients with denture-induced stomatitis, yeast counts usually constituted less than 1% of the total microbial counts. Nonetheless, there was a 10-fold increase in the yeast counts in denture plaque obtained from denture-induced stomatitis patients when compared with healthy controls (Budtz-Jorgensen, 1990).

B. Drug Therapy and Radiation Therapy

It is well known that patients on broad spectrum antimicrobial therapy may be predisposed to alterations in the oral flora. Postantibiotic stomatitis or glossitis caused by *C. albicans* are well recognized (Kennedy and Volz, 1983; Midtvedt, 1990). Topical, systemic, and aerosolized corticosteroids are all important in this respect, and excessive use of antibacterial mouthwashes can also be followed by oral yeast infection (Samaranayake, 1990).

Drugs with xerostomic side effects (such as psychopharmaceuticals) also predispose to oral candidosis (Kostiala *et al.*, 1979). Xerostomia (in Sjögren's syndrome and after radiotherapy) predisposes to marked changes in the oral microbial flora and candidosis (Epstein *et al.*, 1984).

Xerostomia can, in animal models, predispose to candidosis (Jorge *et al.*, 1993).

Longitudinal studies of patients undergoing radiation therapy to the head and neck show significant increases in the numbers of *Candida* species on the surface of the tongue, in whole saliva, and in dental plaque (Brown *et al.*, 1975; Samaranayake *et al.*, 1988).

C. Dietary Factors

A variety of nutritional factors, including deficiencies of iron, folic acid, vitamins and diets rich in carbohydrates, have been implicated in the pathogenesis of oral candidal infections. Cawson (1966) was the first to describe an apparent relationship between iron deficiency and oral candidosis. Cases of chronic mucocutaneous candidosis, chronic atrophic candidosis, angular stomatitis, and atrophic glossitis were reported with iron-deficiency anemia, and the infection was difficult to eradicate as long as the iron deficiency remained (Higgs and Wells, 1972). The iron-dependent *in vitro* growth stimulation of *Candida* is thought to be due to the blocking of the fungistatic property of transferrin, the iron-binding protein present in serum (Esterly *et al.*, 1967). Moreover, iron may also affect the local host defenses via its modulating role in the activity of lysozyme and lactoferrin (Samaranayake, 1990).

Iron deficiency may produce an impairment of iron-dependent enzyme systems, thereby affecting the metabolism and, hence, the kinetics of the rapidly dividing oral epithelial cells (Rennie, MacDonald, and Dagg, 1984). Such alterations may result in an epithelial surface more conducive for the adhesion, growth, and invasion of *Candida* (Jacobs and Lord, 1961). Joynson *et al.* (1972) demonstrated impaired cell-mediated immunity to *C. albicans* in iron-deficient subjects both *in vivo* and *in vitro*, which were restored once the iron levels returned to normal. Other general effects of iron deficiency that may bear a relationship to oral candidosis include deficient phagocytosis and antibody production (Wilton and Lehner, 1981).

Growth of *Candida* either in saliva or nutrient media supplemented with dietary carbohydrates

is accompanied by acid production and a significant concomitant reduction in pH to very low levels (Samaranayake *et al.*, 1983a, 1984a, 1986a; Shepherd and Sullivan, 1976). The reduced pH levels may potentiate candidal virulence by enhancing its growth, multiplication, and adherence to host tissues, while activating the acidic proteases and phospholipases of the yeast. Furthermore, the direct cytotoxic effect of the acidic metabolites may exacerbate the host inflammatory response (Samaranayake and MacFarlane, 1985).

D. Immunologic/Endocrine Disorders

Studies show that *Candida* species are more prevalent in the oral cavity of diabetic patients than in those of healthy nondiabetic individuals. A study by Lamey *et al.* (1988) found no significant difference in the prevalence of oral candidal carriage and infection in diabetic patients vs. nondiabetics in relation to the ability or inability to secrete blood group antigens. Other possible factors such as the ability of *Candida* to adhere to the oral tissue rather than inherited ability to secrete blood group substances may determine those parameters in diabetics. For instance, Darwazeh *et al.* (1990) have recently shown a significant increase in the adhesion of *Candida* to oral epithelial cells of diabetics when compared with a healthy population.

Fungal infections, particularly pseudomembranous and atrophic candidosis, are common in patients with HIV infection and other secondary immunodeficiencies. As a result of depressed cell-mediated immunity or phagocytic immunity, chronic mucocutaneous candidosis (CMC) can also be a feature of primary immune defects such as severe combined immune deficiency syndrome (SCID) (Porter and Scully, 1990). This is fully discussed below.

Chronic hyperplastic candidosis may occur as part of chronic mucocutaneous candidosis, often with identifiable immunologic or endocrine abnormalities as major factors. Endocrine disorders have a familial incidence and are found in children and young adults, particularly in girls. The most frequently associated endocrine manifestations include idiopathic hyperparathyroidism and hypoadrenocorticism, but candidosis follows

only where there is an immune defect (Kostiala *et al.*, 1979).

E. Malignant Diseases

Host defense mechanisms are impaired by the malignant process and its chemotherapy, which in turn can lead to disordered numbers and dysfunction of polymorphonuclear and mononuclear phagocytes and to oral candidosis (Petersen, 1984; Kostiala, 1986).

Acute forms of oral mycoses are frequent in patients with myeloproliferative disease and provide potential sources for fungal septicaemia (Kostiala, 1986; Dreizen *et al.*, 1982). *C. albicans* is isolated in virtually all episodes of fungal stomatitis (Kostiala, 1986).

F. Secretory Status

Correlations between blood groups and vulnerability to infectious diseases, including mycotic infections, are well documented (Bird and Tovey, 1982). Blood group antigens are present on mucosal epithelial cells (Bird and Tovey, 1982) and are found in saliva, gastric secretions, and other body fluids of most individuals (secretors). It has been suggested that the nonsecretion of blood group substances is associated with an increased susceptibility to oral infection with *C. albicans* (Blackwell *et al.*, 1986). The highly significant excess of both blood group O antigen nonsecretion among *C. albicans* carriers suggests it contributes to the oral carriage in healthy subjects. Blackwell *et al.* (1986) found a greater proportion of nonsecretors in patients with oral *C. albicans* infections. Mason, Weber, and Willoughby (1988) also found an excess of nonsecretors among healthy *C. albicans* carriers. The blood group H antigen functions as a *C. albicans* receptor, and, therefore, subjects of blood group O (who possess large quantities of the H antigen on their cell surfaces) are likely to be the most susceptible to candidal colonization and subsequent infection (Mason, Weber, and Willoughby, 1988). In addition, Lewis blood group antigen, found predominantly on the cells of nonsecretors, might act as a receptor for *Candida* species (May, Blackwell, and Weir, 1989).

In a study by Lamey *et al.* (1991), it was suggested that secretor status may be an important factor in the development of chronic hyperplastic candidosis.

VII. CLASSIFICATION AND CLINICAL MANIFESTATIONS OF ORAL *CANDIDA* INFECTIONS

All forms of oral candidosis are considered opportunistic, and the epithet “disease of the diseased” has been applied to these infections. Nevertheless, it is often difficult to identify the exact predisposing factor despite intensive investigations (Samaranayake and Lamey, 1988). This, together with the varied clinical presentation of oral *Candida* infections, has made the task of disease classification somewhat difficult and complicated.

A. Classification

By tradition, the most frequently adopted classification of oral candidosis has been acute pseudomembranous candidosis (thrush), acute atrophic candidosis, chronic hyperplastic candidosis, and chronic atrophic candidosis.

Chronic hyperplastic candidosis was further subdivided into four groups based on localization patterns and endocrine involvement as chronic oral candidosis (candidal leukoplakia), endocrine candidosis syndrome, chronic localized mucocutaneous candidosis, and chronic diffuse candidosis.

Samaranayake and Yaacob (1990) noted that the last subdivision of chronic hyperplastic candidosis generates some confusion, particularly because it lumps together hyperplasias that are localized in the oral cavity alone as well as hyperplasias related to oral manifestations of mucocutaneous candidoses. However, a dichotomous classification that highlights and categorizes candidosis confined to oral and perioral tissues (primary oral candidosis) into one group, and candidal lesions distributed in other parts of the body as well as the oral cavity in another (secondary oral candidosis) may be less confusing.

Basically oral candidosis can be categorized as:

Category I: candidal infections confined to oral and perioral tissues (primary oral candidoses) (Table 4)

Category II: disorders where oral candidosis is a manifestation of generalized systemic mucocutaneous candidal infection (secondary oral candidoses) (Table 5);

Cheilo-candidosis and chronic multifocal candidosis are two further clinical entities that do not fall exactly into any of the candidosis categories.

Cheilo-candidosis presents as a chronic, ulcerative granulating lesion of the vermillion area of the lower lip; chronic multifocal candidosis has been described as causing chronic, erythematous plaque-like lesions in at least two of the following sites: mouth, palate, and dorsum of tongue (Holmstrup and Besserman, 1983; Samaranayake and Lamey, 1988).

Following is a brief account of the clinical variants that comprise primary oral candidoses. Pseudomembranous, erythematous, and hyperplastic candidoses are described first, while *Candida*-associated lesions such as denture-induced stomatitis, angular cheilitis, and median rhomboid glossitis, with a possible fungal and/or bacterial etiology, are described subsequently. Finally, a note on multifocal oral candidosis and systemic *Candida* infections with oral manifestations (i.e., secondary oral candidoses) is given.

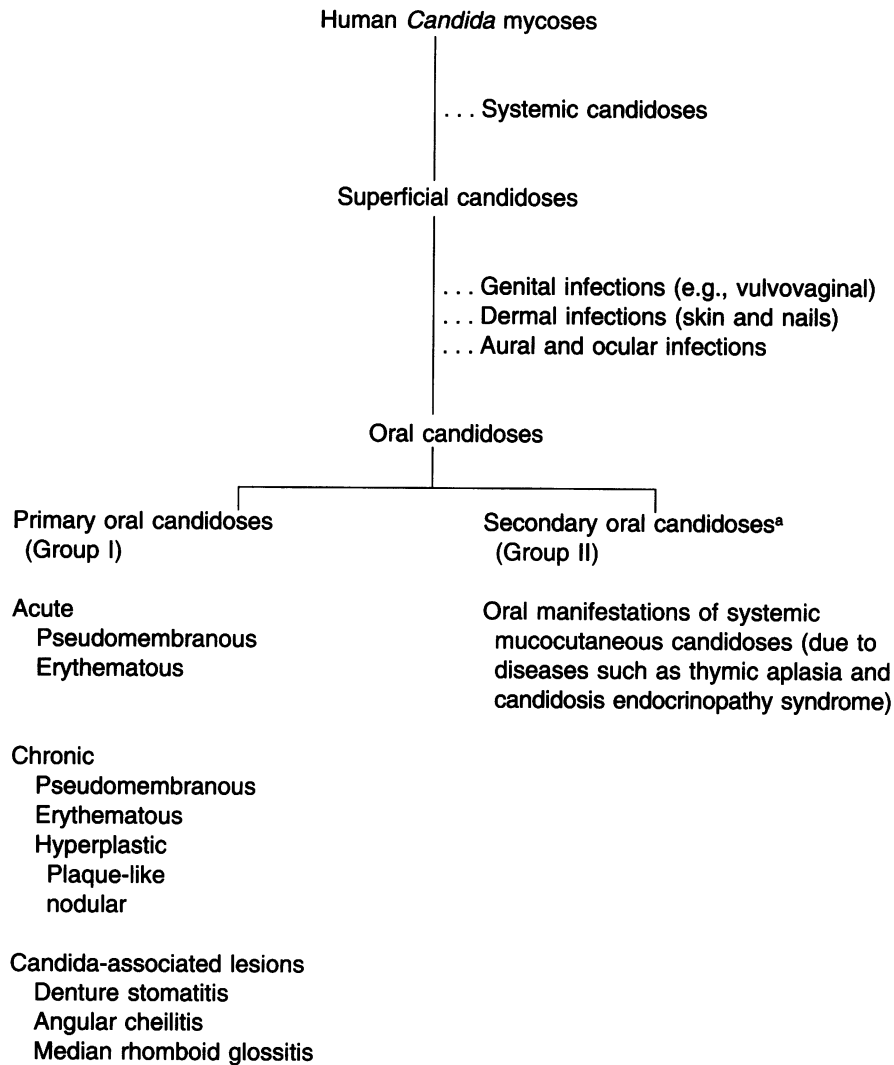
A. Pseudomembranous Candidosis

Oral candidosis in the form of thrush is classically an acute infection, but it may recur for many months or even years in patients using corticosteroids topically or by aerosol, in HIV-infected individuals, and in other immunocompromised patients. The term chronic pseudomembranous candidosis has been used for chronic recurrence of the disease, although this term is not widely accepted (Proceedings of the Second World Workshop in Oral Medicine, Chicago, 1993, in press).

Thrush may be seen in neonates and among terminally ill patients (Finlay, 1986), particularly in association with serious underlying conditions such as leukemia and other malignancies, and is increasingly seen in HIV disease (Kostiala *et al.*, 1982; Samaranayake, 1990b; Scully, 1988).

Thrush is characterized by white patches on the surface of the oral mucosa, tongue, and elsewhere. The lesions develop and form confluent plaques that resemble milk curds and can be wiped

TABLE 4
Classification of Oral Candidosis



^a See Table 5.

From Samaranayake and Yaacob, 1990; Holmstrup and Axell, 1990; Samaranayake, 1991.

off to reveal a raw, erythematous and sometimes bleeding base (Odds, 1988). The plaques in oral thrush are made up of necrotic material and desquamated parakeratotic epithelia, penetrated by *C. albicans* yeast cells and hyphae that invade as far as the stratum spinosum. Edema and microabscesses containing polymorphonuclear leukocytes (PMNL) are found in the outer layers of epithelium. The deeper parts of the epithelium show acanthosis, and the inflammatory response

in the connective tissue comprises lymphocytes, plasma cells, and PMNL (Cawson, 1965; Odds, 1988).

A possible complication of oropharyngeal thrush is the involvement of the adjacent mucosa, particularly those of the upper respiratory tract and the esophagus. The combination of oral and esophageal candidosis is particularly prevalent in HIV-infected patients (Holmstrup and Samaranayake, 1990).

TABLE 5
Classification of Oral Candidosis

Subgroup	Condition	Onset	Affected sites and clinical features
1	Familial chronic mucocutaneous candidosis	First decade of life	Mouth, nails, skin, mainly chronic hyperplastic lesions
2	Diffuse chronic mucocutaneous candidosis	Before 5 years of age	Mouth, nails, skin, eyes, pharynx and larynx: chronic hyperplastic lesions
3	Candidosis endocrinopathy syndrome	By second decade	Mouth: associated with hypoparathyroidism, hypothyroidism, hypoadrenocorticism and diabetes mellitus; chronic hyperplastic lesions
4	Familial mucocutaneous candosis	In the first year of life	Mouth, nails, scalp, flexures; chronic hyperplastic lesions
5a	Severe combined immunodeficiency	Childhood	Oral mucosa, skin, nails; pseudomembraneous or hyperplastic lesions
5b	Di George's syndrome		
5c	Chronic granulomatous disease		
6	Acquired immunodeficiency syndrome (AIDS)	Any age	Oral mucosa, esophagus; may manifest as pseudomembraneous, erythematous, or hyperplastic lesions

Note: Group II: These are rare disorders (except Subgroup 6), where candidosis remains superficial; patients usually do not die from disseminated candidosis.

B. Erythematous (Atrophic) Candidosis

Erythematous or atrophic candidosis is an uncommon and poorly understood condition associated with corticosteroids and topical or systemic broad spectrum antibiotics or HIV disease. It may arise as a consequence of persistent acute pseudomembranous candidosis when the pseudomembranes are shed, may develop *de novo* (Lehner, 1967), or in HIV infection may precede pseudomembranous candidosis (Pindborg and Nielsen, 1989).

The clinical presentation is characterized by erythematous areas generally on the dorsum of the tongue, palate, or buccal mucosa. Lesions on the dorsum of the tongue present as depapillated areas. Red areas are often seen in the palate in

HIV disease. There can be an associated angular stomatitis (Kostiala *et al.*, 1979).

Holmstrup and Axell (1990) noted that the term “atrophic” used to describe the red areas could be a misnomer, as redness may be caused not only by reduced epithelial thickness — atrophy — but also by increased vascularity. Hence, they suggested that the term “atrophic candidosis” should be replaced by “erythematous candidosis” in a new classification of oral candidosis (Holmstrup and Axell, 1990).

C. Hyperplastic Candidosis (*Candida* Leukoplakia)

Candida leukoplakias are chronic, discrete raised lesions that vary from small, palpable, trans-

lucent, whitish areas to large, dense, opaque plaques, hard and rough to the touch (plaque-like lesions). Homogeneous areas or speckled areas can be seen, which do not rub off (nodular lesions). Speckled leukoplakia counts for 3 to 50% of all candidal leukoplakias, and they are often symptomatic. *Candida* leukoplakias usually occur on the inside surface of one or both cheeks, less often on the tongue (Cawson and Lehner, 1968; Arendorf *et al.*, 1983). Biopsy is important, as the condition is premalignant and shows varying degrees of dysplasia (Samaranayake, 1990a; Daftary *et al.*, 1972). Oral cancer supervenes in 9 to 40% of candidal leukoplakias compared with the 2 to 6% risk of malignant transformation cited for leukoplakias in general (Banoczy, 1977). The risk of carcinoma developing in candidal leukoplakia will depend on whether the lesion is speckled or homogeneous, the presence and degree of epithelial dysplasia, and the management adopted (Field *et al.*, 1989).

The histopathology of candidal leukoplakia includes parakeratosis and epithelial hyperplasia and *Candida* invasion restricted to the upper layers of epithelium (Arendorf *et al.*, 1983; Daniels *et al.*, 1985). In a minority of cases, the condition has been associated with iron and folate deficiencies and with defective cell-mediated immunity (Jenkins *et al.*, 1977; Walker and Arendorf, 1990).

D. *Candida*-Associated Denture Stomatitis (Denture-Induced Stomatitis, Denture Sore Mouth, Chronic Atrophic Candidosis)

The characteristic presenting signs of denture-induced stomatitis are chronic erythema and edema of the mucosa that contacts the fitting surface of the denture. The mucosa below lower dentures is hardly ever involved.

The patient may occasionally experience slight soreness but is usually free of symptoms. The only presenting complaint may be an associated angular stomatitis (Scully, 1986). Dorey and Blasberg (1985) found that 28% of patients were aware of a burning or tingling sensation under dentures, but the remainder were asymptomatic.

Newton (1962) classified denture-induced stomatitis into three clinical types: type I, a local-

ized simple inflammation or a pinpoint hyperaemia; type II, an erythematous or generalized simple type presenting as more diffuse erythema involving a part of, or the entire, denture-covered mucosa, and type III, a granular type (inflammatory papillary hyperplasia) commonly involving the central part of the hard palate and the alveolar ridge.

Histologic examination of the soft tissue beneath dentures has shown proliferative or degenerative responses (Razek and Shaaban, 1978) with reduced keratinization and thinner epithelium (Watson and MacDonald, 1982). Dentures can also produce other changes: the oral flora may be altered and plaque collects between the mucosal surface of the denture and the palate. In addition, the saliva that is present between the maxillary denture and the mucosa may have a lower pH than usual (Burket, 1977).

The generalized simple and the granular types of denture-induced stomatitis are most often caused by the accumulation of microbial plaque (bacteria or yeasts) on and in the fitting surface of the denture and the underlying mucosa (Arendorf and Walker, 1979; Budtz-Jorgensen, 1974). When *Candida* is involved, the more common terms "*Candida*-associated denture stomatitis", "denture-induced candidosis", or "chronic atrophic candidosis" are used. Denture-induced stomatitis is not exclusively associated with *Candida*, however, and, occasionally, other factors such as bacterial infection, mechanical irritation, or an allergic reaction to the denture base material may be implicated (Budtz-Jorgensen, 1990). Nonetheless, there are no clinical criteria that can reliably distinguish between a *Candida*-associated, a bacterial-induced, a trauma-induced denture stomatitis, or an allergic reaction to the denture base material (Budtz-Jorgensen, 1990). The high proportion of women to men sufferers is more likely because of the higher incidence of edentulism among women and because of the tendency for women to seek dental treatment more often than men (Dorey and Blasberg, 1985).

Patients with denture-induced stomatitis do not have any serious cell-mediated immune defects, but they may be deficient in migration-inhibition factor and may have overactive suppressor T cells or other T-lymphocyte/phagocyte defects (Iacopino and Wathen, 1992).

E. Angular Stomatitis (Perleche, Angular Cheilitis)

This is a clinical diagnosis of lesions that affect the angles of the mouth, characterized by soreness, erythema, and fissuring, and is commonly associated with denture-induced stomatitis (Cawson, 1966; Budtz-Jorgensen, 1990). Both yeasts and bacteria (especially *Staphylococcus aureus*) are involved, as interacting, predisposing factors (Cawson, 1966; Budtz-Jorgensen, 1974; Warnakulasuriya, Samaranayake and Peiris, 1991). However, angular stomatitis is, very occasionally, an isolated initial sign of anemia or vitamin deficiency, such as vitamin B12 deficiency, and resolves when the underlying disease has been treated (Scully and Cawson, 1987). Iron deficiency anemia and other vitamin deficiencies have been cited as other predisposing factors (Samaranayake, 1986). In uncommon conditions, such as orofacial granulomatosis, up to 20% of individuals have angular stomatitis, although *Candida* species are not often isolated (Samaranayake and Lamey, 1988). Angular stomatitis may also be seen in HIV disease (Samaranayake and Holmstrup, 1989).

Few authors consider that the lesion results solely from maceration due to deep, occlusive folds of skin at the mouth angles in individuals with facial height reduced by old age or edentia (Chernosky, 1966).

F. Median Rhomboid Glossitis

Midline glossitis, or glossal central papillary atrophy, is characterized by an area of papillary atrophy that is elliptical or rhomboid in shape, symmetrically placed centrally at the midline of the tongue, anterior to the circumvallate papillae. Occasionally, median rhomboid glossitis presents with a hyperplastic exophytic or even lobulated appearance. The relevance of *Candida* to the condition has been controversial, with some authors claiming that the *Candida* causes the condition, particularly the papillary atrophy (Tapper-Jones *et al.*, 1980). Histopathologically, candidal hyphae infiltrate the superficial layers of the parakeratotic epithelium and a polymorphonuclear leukocyte infiltrate occupies the epithelium, with

elongated hyperplastic rete ridges and a lymphocyte infiltration in the corium (Walker and Arendorf, 1990). However, it has been demonstrated that the condition frequently shows a mixed bacterial/fungal microflora (Escobar, Farman, and Arm, 1984).

G. Chronic Multifocal Oral Candidosis

This term has been given to chronic candidal infection that may be seen in multiple oral sites, with various combinations, including (1) angular stomatitis that is unilateral or bilateral and encountered mainly in denture wearers, (2) retrocommissural leukoplakia that is the most constant component of the tetrad, (3) median rhomboid glossitis, and (4) palatal lesions (Cernea *et al.*, 1965; Holmstrup and Besserman, 1983). Holmstrup and Bessermann (1983) applied the additional criteria: (1) lesions of more than 1 month duration; (2) an absence of predisposing medical conditions; (3) patients who had received radiotherapy or drugs of the following types were also excluded: antibiotics, antiinflammatory or immunosuppressive drugs, and cytotoxic or psychotropic agents.

Most patients are adult males and tobacco smokers in their fifth or sixth decade at presentation (Cernea *et al.*, 1965; Pindborg, 1980). Antifungal therapy will clear the infection and produce clinical improvement, but recurrence is common, unless smoking can be reduced (Holmstrup and Bessermann, 1983).

H. Oral Candidosis Associated with Systemic Infections

Candidosis is usually restricted to the skin and mucous membranes but may occasionally spread. Systemic forms of candidosis may affect only one organ or be disseminated (*Candida* septicaemia) hematogenously (Odds, 1988). Whereas the candidoses included in Table 4 (Group I) are limited mainly to the oral cavity, it is important to recognize that oral candidal infection can occasionally manifest as a result of systemic complications (Group II or secondary oral candidoses, Table 5) (Bodey and Anaissie, 1989).

In immunocompromised patients, however, it is clear that the majority of patients with candidaemia have evidence of invasive infection. For example, up to 30% of all patients with acute leukemia die with systemic *Candida* infections (Carpentier, Kiehn, and Armstrong, 1981). The usual presentation is a patient with persistent fever unresponsive to broad-spectrum antibacterial antibiotics (Odds, 1988).

VIII. CANDIDOSIS AND IMMUNOCOMPROMISED HOSTS

A few patients have chronic candidosis from an early age, sometimes with a defineable immune defect (e.g., chronic mucocutaneous candidosis). The number of patients immunocompromised by diseases such as HIV infection, hematological malignancy, and treatment protocols, including aggressive cytotoxic therapy, however, has increased during recent years and comprises by far the largest such group.

A. Chronic Mucocutaneous Candidosis (CMC)

CMC is the term given to the group of rare syndromes, sometimes with a defineable immune defect, in which there is persistent mucocutaneous candidosis that responds poorly to topical treatment. In general the more severe the

candidosis, the greater the likelihood that immunological defects (particularly of cell-mediated immunity) can be identified (Scully, 1988). The main types of these rare disorders and their features are shown in Table 6 (Scully and Cawson, 1987). Further details are given elsewhere (Porter and Scully, 1990; Scully and Cawson, 1987).

B. HIV-Related Oral Candidosis

Candida infections, with oral thrush and esophagitis as frequent clinical manifestations, are the most common opportunistic infections encountered in AIDS (Klein *et al.*, 1984; Holmberg and Meyer, 1986; Samaranayake and Scully, 1989). Ever since the first clinical definition of AIDS (1981), the CDC/WHO have recognized candidosis of the mouth, oesophagus, trachea, bronchi, and lungs as "major" opportunistic infections and important indicator diseases.

Subsequently, in 1986 the Walter Reed Army Institute of Research (Redfield *et al.*, 1986) adopted a staging classification of HIV infection, applicable to adults only, based on HIV-antibodies and virus isolation, chronic lymphadenopathy, T-helper cells/mm³, delayed hypersensitivity, appearance of thrush, and other opportunistic infections (Drouhet and Dupont, 1991).

Also, it has been shown in prospective studies of HIV-infected patients that the occurrence of an otherwise unexpected mycosis (typically oral candidosis) in an HIV-infected individual can be

TABLE 6
Chronic Mucocutaneous Candidosis Syndromes

Type	Clinical features
Familial CMC	Persistent oral candidosis Iron deficiency
Diffuse CMC (<i>Candida</i> granuloma)	Severe chronic candidosis Susceptibility to bacterial infections
Candidosis-endocrinopathy syndrome	Mild chronic candidosis Hypoparathyroidism Hypoadrenocorticism
Candidosis thymoma syndrome	Chronic candidosis Myasthenia gravis Hematological disorders

From Scully, C. and R. Cawson, 1987.

predictive of the subsequent development of full-blown AIDS (Klein *et al.*, 1984; Sabin *et al.*, 1992).

Retrospective studies have shown that at least 58 to 81% of all AIDS patients contract a fungal infection at some time, and 10 to 20% die as a direct consequence (Holmberg and Myer, 1986). Clearly, *Candida* infections appear to be the most common fungal infection, occurring in at least 75% of HIV-infected patients (Scully *et al.*, 1990). McCarthy *et al.* (1991) have shown that 92% of patients with a diagnosis of AIDS had oral candidosis, compared with only 24% of HIV-infected patients who had not developed AIDS.

1. Factors Associated with Increased Frequency of HIV-Related Oral Candidosis

The main cause of infection in HIV disease is the immune impairment, but candidosis is found approximately three times more frequently in patients who also have xerostomia (McCarthy *et al.*, 1991).

Recent studies have shown that oral Langerhans cells are infected by HIV (Braathen *et al.*, 1987) and may also play a role in candidosis. *Candida* itself may also induce immunosuppression, and this can influence the prognosis of HIV infection (Odds, 1988).

2. Clinical Variants of Oral Candidosis in HIV Infection

The manifestations of candidal infections in HIV infection are usually restricted to superficial candidosis with varying degrees of severity. Although not life-threatening, these infections are persistent and debilitating (Holmberg and Meyer, 1986). The major clinical variants of oral candidosis, namely pseudomembranous, erythematous, and hyperplastic candidoses, have all been described in HIV-infected individuals, and it should be stressed that their clinical presentation is similar to those who are not infected with HIV.

Thrush (pseudomembranous candidosis), the most immediately clinically obvious type of

candidosis, may involve any area of the oral mucosa, but most frequently the tongue, hard and soft palate, and buccal mucosa. Oral thrush can manifest for a variable time period prior to the development of Kaposi's sarcoma or other life-threatening opportunistic infections (Scully *et al.*, 1990; Holmberg and Meyer, 1986).

The erythematous (atrophic) type of oral candidosis is found predominantly in the palatal mucosa and dorsum of the tongue (Scully *et al.*, 1990; Samaranayake and Holmstrup, 1989). Some have suggested that erythematous candidosis is as serious a prognostic indicator as pseudomembranous candidosis, because the erythematous form is more difficult to recognize and, hence, is underdiagnosed (Dodd *et al.*, 1991).

Esophageal candidosis in a person with no other known cause for diminished resistance to the disease is also considered indicative of AIDS (Centers for Disease Control/Classification, 1985). Esophageal candidosis is notable for its persistence, but dissemination does not appear to result (Armstrong *et al.*, 1985). Esophageal candidosis gives rise to dysphagia and retrosternal discomfort and, in some, tenderness on pressing on the sternum. Lack of esophageal symptoms in a patient with AIDS and oral candidosis does not, however, exclude esophageal involvement (Holmberg and Meyer, 1986), which can be diagnosed by endoscopy (Tavitian *et al.*, 1986).

Also, candidosis presenting as median rhomboid glossitis is not uncommon in HIV disease. Angular stomatitis is not infrequent and its appearance in a nondenture wearer, particularly if in a high-risk group or if it is recalcitrant to treatment, now raises the suspicion of the presence of HIV or other immune defects (Scully *et al.*, 1990; Samaranayake, 1990b).

Oral candidosis appears also to be a frequent sign of HIV infection in children. Most children with perinatal HIV infection develop mucocutaneous candidosis in the first year of life, as opposed to a small percentage of children who are diagnosed after this period as having AIDS. Therefore, in the young infants with HIV infection, chronic mucocutaneous candidosis may act as a warning sign for early and severe morbidity (Selik, Stracher, and Curran, 1988; Samaranayake, 1990b).

Histologically, oral candidal infection in HIV-infected patients frequently shows a remarkably weak inflammatory reaction; the epithelium may be invaded by numerous hyphae or pseudohyphae without the usual characteristic massive infiltrate of polymorphonuclear leukocytes. Likewise, the subepithelial inflammatory reaction is sparse and contains few or no leukocytes (Greenspan *et al.*, 1986).

IX. THE POSSIBLE ROLE OF *CANDIDA* IN ORAL CARCINOGENESIS

Candida-involved leukoplakias (keratoses) are often of the nonhomogeneous types (Roed-Petersen *et al.*, 1970) and untreated, 5 to 10% may develop into carcinomas (Pindborg, 1980). However, although the epithelium of the leukoplakias is invaded by *Candida* it is unclear whether the yeasts are causally involved in the development or transformation of leukoplakia.

Candida albicans is, by far, the species most commonly isolated, and the biotypes associated with leukoplakias differ from those isolated from normal oral cavities (Jepsen and Winther, 1965; Krogh *et al.*, 1987; Krogh, 1990). *Candida* types from nonhomogeneous leukoplakia have higher nitrosation potentials than others, which might indicate a possible role of specific types in the transformation of some leukoplakias (Krogh, 1990). *Candida* species may be involved in carcinogenesis by elaborating nitrosamine compounds (Blank *et al.*, 1968; Krogh *et al.*, 1987), which act either directly on the oral mucosa or interact with other chemical carcinogens to activate specified protooncogenes and thereby initiate oral neoplasia (Field *et al.*, 1989).

Candida leukoplakia is characterized histologically by chronic intraepithelial inflammation with fungal hyphae invading the superficial layers of the epithelium (Cawson and Lehner, 1968). The cellular changes often include hyperplasia, cellular atypia, mild or severe dysplasia, and *in situ* or invasive carcinoma (Cawson and Lehner, 1968; Pindborg, 1971; Roed-Petersen *et al.*, 1970).

Candida may produce preneoplastic changes in the oral mucosa in animal models (Franklin and Martin, 1986) and can act as a tumor promoter (O'Grady and Reade, 1992).

X. LABORATORY DIAGNOSIS OF ORAL CANDIDOSIS

Systems for identification of yeasts may range from a few simple tests useful in speciating *C. albicans* to a large battery of tests that enables differentiation of all yeasts of medical and dental importance. Identification is best accomplished by using a combination of morphologic features and biochemical characteristics.

A. Microbiology

Any kind of clinical material (swab, sputum, etc.) for microscopy or culture should be examined as quickly as possible, because drying may impair the viability of yeasts. As quantitative assessment is an important factor in the differentiation between carriers and infected patients, specimens must be dealt with immediately, or kept in transport medium and stored in a refrigerator, for a maximum period of 24 h. When the clinical material is received in the laboratory, it is plated on a suitable culture medium. Frequently, Sabouraud's dextrose agar is used as a primary culture medium, although it rarely permits distinction between different yeast species (Silverman *et al.*, 1990). For the latter purpose, Pagano-Levin medium is useful (Samaranayake, MacFarlane, and Williamson, 1987).

1. Smears

Detection of yeasts in a clinical specimen should start with direct microscopic examination of smears from the lesion. After fixation, one slide is stained by the Gram stain and the other by the periodic acid Schiff (PAS) technique. Yeast cells appear dark blue after Gram staining and red or purple in PAS preparations (Silverman *et al.*, 1990).

2. Swab

Rubbing a sterile cotton-tipped swab over the lesional tissue or all surfaces irrespective of the clinical signs is a useful assay for the presence or

absence of *Candida*, but it cannot provide a quantitative estimate (Silverman *et al.*, 1990).

3. Imprint Culture Technique

This technique uses a sterile plastic foam pad of known size (typically 2.5×2.5 cm) dipped in Sabouraud's broth and placed on the suspect mucosal surface for 60 s. Then the plastic foam is placed directly on Sabouraud's or Pagano-Levin agar. *Candida* density at each site is determined by a Gallenkamp colony counter and expressed as colony-forming units per mm² (CFU mm²) (Arendorf and Walker, 1979). Arendorf and Walker (1979), using the imprint culture technique, surmized that the technique could also be used to discriminate between the carrier state and oral candidosis. Thus, according to these workers, colony counts in excess of 30 CFU cm² of mucosa in the dentate and 49 CFU cm² in denture wearers suggested a candidal infection.

4. Paper Points

C. albicans has been detected previously in high numbers in the subgingival flora (Slots *et al.*, 1988) or in the gingival tissues of acute periodontal abscesses (Peterson *et al.*, 1987). An absorbent sterile paper point is inserted to the depth of the pocket and then transferred to a transport medium (Olsen, 1990). The latter is then whirlimixed thoroughly, in the laboratory and plated out on appropriate media.

5. Salivary Culture Technique

This involves requesting the patient to expectorate about 2 ml of mixed unstimulated saliva into a sterile, universal container. The number of *Candida* expressed as CFU per milliliter of saliva is estimated by counting the resultant growth on Sabouraud's agar (Silverman *et al.*, 1990).

Epstein, Pearsall, and Truelove (1980) have shown that the quantitative culture of saliva is a useful adjunct in diagnosis of oral candidosis. They demonstrated that carriers and patients with oral *Candida* can be distinguished reliably (with

95% confidence limits) on the basis of quantitative culture. Patients with clinical candidosis harbor greater than 400 CFU of *Candida* per milliliter of saliva (Epstein, Pearsall, and Truelove, 1980).

6. Oral Rinse Technique

This consists of requesting the patient to rinse the mouth for 60 s with 10 ml of sterile phosphate-buffered saline (PBS, pH 7.2) or sterile water. The patient then returns the oral rinse to the universal container. If the patient wears a denture, this should be removed prior to sampling. The oral rinse is centrifuged at $1700 \times g$ for 10 min, and the deposit resuspended in 1 ml of sterile PBS. The concentrated oral rinse is now inoculated on appropriate media to assess CFU per milliliter of rinse sample using a Spiral Plater prior to incubation. The CFU (estimated using a Gallenkamp colony counter) is multiplied by the dilution factor to yield the CFU per milliliter of original oral rinse sample (Samaranayake *et al.*, 1986b).

The concentrated oral rinse culture technique has a number of advantages over the imprint technique. It is simple to perform as it does not involve the clinician in judgement of the sampling site. In addition to *Candida* species, a single rinse sample can be used for quantitation of other organisms such as coliforms (Samaranayake *et al.*, 1986b).

7. Commercial Systems

A rapid commercial system (Microstix-*Candida* and Oricult-N) for diagnosing oral candidosis is useful for screening patients in the clinical setting, particularly when microbiology laboratories are not within easy access (Silverman *et al.*, 1990).

B. Histopathology

Although swabs and smears are essential for a microbiological diagnosis of a number of types of oral candidosis when candidal leukoplakia (chronic hyperplastic candidosis) is suspected, a

biopsy specimen should be taken. Because *Candida* species stain poorly by hematoxylin and eosin, staining with periodic acid Schiff (PAS) or Gridley's or Gomori's methenamine silver (GMS) stains are used. In both Gridley's and the PAS procedure, the fungi appear a pinkish-red. The GMS technique stains yeast cell walls brown-black because of deposition of reduced silver. The presence of blastospores and characteristic pseudohyphae or hyphae in the superficial epithelial tissues identifies the fungus as a species of *Candida*. However, as the speciation of the organism cannot be performed by this means alone, cultural studies should also be used (Silverman *et al.*, 1990).

Blastospores similar to those of *Candida* species may be seen in histoplasmosis or cryptococcosis, both of which are becoming increasingly important and may manifest orally with increasing frequency in AIDS patients (Greenspan *et al.*, 1986). Therefore, if only blastospores of *Candida* are seen in tissue sections of suspect patients, serial sections should be carefully searched for pseudohyphae or hyphae of *Candida* species (Silverman *et al.*, 1990).

C. Immunologic Tests

Immunity in superficial candidosis and in oral candidosis is predominantly cell mediated (Budtz-Jorgensen, 1990). Cell-mediated immunity to *C. albicans* antigens can be demonstrated in most human subjects both by the appearance of delayed skin hypersensitivity to *Candida* antigens and by *in vitro* tests of cellular immunity such as inhibition of leukocyte migration or stimulation of lymphocyte transformation to *Candida* antigens (Odds, 1988).

As tests of humoral immunity, the *Candida* agglutinin test, the *Candida* complement fixation test, the *Candida* precipitin test, immunofluorescence, and ELISA tests have been used. In the serological tests, four principal types of *Candida* antigens have been used, namely, whole nonviable yeast cells, *Candida* culture filtrates, cell wall polysaccharides or glycoproteins, and cytoplasmic antigens from mechanically disrupted yeast cells. Serologic tests for *Candida*, however, are not diagnostic tools, as the diagnosis can be achieved more readily by clinical evaluation and

by smear or culture (Odds, 1988; Jeganathan and Chan, 1992).

D. Hematologic Investigations

Because oral candidosis is associated frequently with predisposing factors such as nutritional deficiencies, blood dyscrasias or HIV disease, estimates of hemoglobin, lymphocyte and white blood cell counts, corrected whole blood folate, vitamin B12 and serum ferritin can be important (Scully and Cawson, 1987).

Tests such as lymphocyte function, serum immunoglobulins, calcium status, or parathyroid hormone levels are unnecessary except in chronic mucocutaneous candidosis. Because some endocrine disorders may be associated with oral candidosis, tests of thyroid or adrenocortical function are warranted in selected individuals (Lamey and Samaranayake, 1988).

XI. PROPHYLAXIS OF ORAL CANDIDOSIS

Those at greatest risk of fungal infection are patients with HIV disease, receiving cancer chemotherapy, immunosuppressive therapy, or prolonged antibiotic therapy.

Often in the treatment of fungal infection attention to the underlying cause will avoid the need for prolonged or repeated courses of treatment. If antibiotics or corticosteroids (oral or inhaled) are the probable cause, reducing the dose or changing the treatment may help. Intermittent or prolonged topical treatment may be necessary where the underlying cause is unavoidable or incurable (Drug and Therapeutics Bulletin, 1990).

In patients with severe immunosuppression, prevention of colonization and infection is the goal because the oropharyngeal region may be the primary source of initial colonization and allow subsequent spread of the infection. In HIV infection, topical agents will often control the infection initially until the increasing immune defect necessitates systemic agents (Epstein, 1990).

Topical antifungal agents are available as rinses, tablets, vaginal tablets, and creams. Oral rinses are useful for patients with dry mouth who may have difficulty in dissolving tablets. How-

ever, some oral products are sweetened with sugar, thus predisposing to dental caries (Epstein, 1990).

Denture plaque often contains *Candida* species. Therefore, to prevent denture-induced stomatitis, denture cleansing that includes removal of *Candida* is a necessary and important factor (Olsen, 1974; Budtz-Jorgensen, 1974). Cleansers can be divided into groups according to their main components: alkaline peroxides, alkaline hypochlorites, acids, disinfectants, and enzymes (Budtz-Jorgensen, 1990).

Yeast lytic enzymes and proteolytic enzymes are found to be the most effective against candida (Tamamoto *et al.*, 1985). Denture soak solution containing benzoic acid completely eradicates *C. albicans* from the denture surface as it is taken up into the acrylic resin and eliminates the organism from the internal surface of the prosthesis (Iacopino and Wathen, 1992). Kamalakshi *et al.* (1992) have shown the effectiveness of an oral rinse containing 0.12% chlorhexidine gluconate in complete elimination of *C. albicans* from the acrylic resin surface of the denture, and in reduction of palatal inflammation. A protease-containing denture soak (alcalase protease) is also an effective way of removing denture plaque, especially when combined with brushing (Odman, 1992).

XII. TREATMENT OF ORAL CANDIDOSIS

Antifungal chemotherapy has been reviewed recently (van den Bossche, 1991; Graybill, 1992; Rinaldi, 1992).

A. Polyene Antifungal Agents

The polyene agents are derived from *Streptomyces* species; they include nystatin and amphotericin (Epstein, 1990; Lewis *et al.*, 1991).

1. Nystatin

Nystatin was the first specific polyene antifungal agent effective in the treatment of candidosis. Nystatin, if swallowed, may lead occasionally to gastrointestinal side effects such as nausea, vomiting, and diarrhea (Epstein, 1990;

Lewis *et al.*, 1991; Drug and Therapeutics Bulletin, 1990). However, when given parenterally, the toxicity and insolubility have limited it to topical use in a rinse form, oral and vaginal tablets or creams. The medications have to be applied four times daily, 500,000 units for adults and 100,000 for children. Higher doses may be required in immunocompromised patients.

2. Amphotericin

Amphotericin binds to the membrane sterols of fungal cells, causing impairment of their barrier function and loss of cell constituents (Warnock, 1991). It has a broad spectrum of action that includes most of the major fungal pathogens of man.

The use of amphotericin for oral infections is usually limited to topical application (oral suspension 100 mg/ml, lozenges 10 mg) (Epstein, 1990; Lewis *et al.*, 1991; Drug and Therapeutics Bulletin, 1990). Occasional strains of *C. albicans* resistant to amphotericin are now being reported (Conly *et al.*, 1992).

Amphotericin is not absorbed from the gut, and although it can be given intravenously (for systemic candidosis) there is a considerable risk of toxicity, which may manifest as fever, vomiting, and renal, bone marrow, cardiovascular, and neurological toxicity.

B. Azole Agents

These synthetic antifungals, subdivided into imidazoles and triazoles, are the first broad spectrum agents active against a number of yeasts. Their fungistatic property is due to the changes in the permeability of the yeast cell cytoplasmic membranes. The currently available imidazoles are clotrimazole, miconazole, econazole, and ketoconazole, while fluconazole and itraconazole are the more recently introduced triazoles (Epstein, 1990; Bodey, 1992).

1. Clotrimazole

Clotrimazole may be the most potent topical agent in this class of antifungals but is used as a

topical agent only because of its gastrointestinal and neurological toxicity (Odds, 1988).

2. Miconazole

Miconazole is used mainly for topical treatment of candidosis. It is available for parenteral use against systemic mycoses, but the injection contains polyethoxylate castor oil, which may provoke allergic reactions (Bodey, 1992).

3. Ketoconazole

Ketoconazole was the first of the imidazole agents shown to be capable of achieving therapeutic blood levels when given orally. This led to the drug being used in the treatment of CMC and candidosis in immunocompromised patients, but adverse effects, including nausea, rashes, pruritus, and hepatotoxicity, have restricted its use (Brass *et al.*, 1982).

4. Fluconazole

Fluconazole is a recently introduced *bis*-triazole antifungal that acts by inhibiting fungal ergosterol production essential in cell wall formation (Bammer *et al.*, 1990). Fluconazole inhibits the cytochrome c-dependent demethylation step in the formation of ergosterol in the cell membrane. Fluconazole has little affinity for mammalian cytochromes, which is thought to explain its apparently low toxicity (Hay, 1990a, 1990b).

Adhesion of *Candida* to epithelial cells, widely recognized as the essential step in the process of candidal colonization and subsequent infection (Kennedy, 1988) is also significantly inhibited by fluconazole (Darwazeh *et al.*, 1991). Because fluconazole is secreted in saliva in high concentration, it is tempting to speculate that fluconazole may interfere with the synthesis or structure of *Candida* receptors on buccal epithelial cells (Farrow, 1987).

Oral absorption of fluconazole is rapid and nearly complete within 2 h (Washton, 1989). Intravenous preparations are available for patients who cannot take medication by mouth. Fluconazole appears to undergo relatively little metabo-

lism in the body, elimination being predominantly renal (Brammer *et al.*, 1990; Hay, 1990). With normal renal function, the serum half-life is approximately 30 h. The concentration of drug in the CSF is estimated to be between 50 to 90% plasma concentration. All this suggests that fluconazole is best given once daily and will penetrate into CSF and urine in high concentration (Humphrey *et al.*, 1985).

Oral fluconazole has generally been well tolerated and, with usual doses, does not appear to suppress the synthesis of corticosteroid hormones. Elevated plasma concentration of tolbutamide, phenytoin, and warfarin have been observed after fluconazole administration, but without significant effects (Breckenridge, 1992). Although serious cutaneous reactions and hepatitis have occurred in a few patients receiving fluconazole, these reactions appear to be infrequent and may not be related to the fluconazole at all (Galgiani, 1990), although in a study by Franklin *et al.* (1990), jaundice and abnormal liver function tests were seen in some patients treated with fluconazole for HIV-related oral candidal infection. Wells and Lever (1992) reported a patient with AIDS-related oropharyngeal candidosis treated with fluconazole who developed a dose-related liver dysfunction.

In patients with chronic atrophic oral candidosis, fluconazole is effective, particularly when administered concurrently with an oral antiseptic such as chlorhexidine (Hay, 1990b). In patients with chronic mucocutaneous candidosis in whom relapses after initial remission are expected, fluconazole in a dose of 50 mg produced beneficial clinical and mycological responses in a mean period of 10 d (Hay, 1990b).

The efficacy and toxicity of fluconazole 50 mg daily was compared with ketoconazole 200 mg daily in a randomized prospective, double-blind evaluation of patients with either AIDS or AIDS-related complex. Infection was eradicated in all patients treated with fluconazole, but in only 75% of the patients who were given ketoconazole (de Wit *et al.*, 1989). It would seem that the regime of 50 mg per day (single dose therapy) of fluconazole for a period of 2 to 3 weeks may be adequate to prevent or suppress candidosis in HIV-infected patients. Indeed, 50 mg per day is the dose recommended by the drug manufacturers for the treatment of oral candidosis. Nevertheless,

either maintenance therapy or intermittent therapy with fluconazole is essential to prevent relapse after cessation of treatment (Lewis *et al.*, 1991).

AIDS patients treated with fluconazole 200 mg/d orally for approximately 3 weeks had recurrence of oral and pharyngeal candidosis after the therapy was stopped. When the fluconazole therapy was started again at the same dosage as before, the patients had an incomplete response (Lucatorto *et al.*, 1991).

Patients undergoing therapy for metastatic malignancy were randomly assigned to receive fluconazole or placebo as antifungal prophylaxis. Oropharyngeal candidosis developed in only 2% of patients receiving fluconazole but in 28% of patients receiving placebo. The favorable results from this study indicate that fluconazole should be evaluated as antifungal prophylaxis in patients at greatest risk of developing serious fungal infections, such as transplant patients or those receiving chemotherapy for malignant diseases (Bodey *et al.*, 1990).

5. Itraconazole

This is an orally active *bis*-triazole, similar to fluconazole, which inhibits ergosterol biosynthesis in the fungal cell. It has a long half-life and fewer side effects than ketoconazole but is expensive (Jansen *et al.*, 1991) and is eliminated hepatically. Its use is contraindicated in liver disease. It is available in 50 and 100 mg capsules and 10 mg/ml oral solution. For a period of 2 weeks 100 to 200 mg/d gives good clinical and laboratory results compared with ketoconazole and clotrimazole (Smith *et al.*, 1991b; Blatchford, 1990).

The availability of an oral solution may offer advantages over capsules because it will be easier to swallow for patients with oral candidosis and for administration by nasogastric tube (Blatchford, 1990).

6. Drawbacks of the Azoles

All the azoles (i.e., the imidazoles and triazoles) are fungistatic, not fungicidal. This is an important consideration when treating the chronically immunosuppressed, such as those with

AIDS, and when treating infections at critical sites, such as candidal meningitis and failures to respond to triazoles such as fluconazole (Siegmán-Igra and Raban, 1992). None of the azoles are entirely benign and they are expensive. Hepatotoxicity may be common to all of them, and the potential for endocrine toxicities exists, particularly at high doses. Furthermore, as with any new agent, novel toxicities may yet be discovered (Graybill, 1989).

The introduction of any new antimicrobial is almost always associated with the emergence of resistant flora (Ayliffe, 1979). As far as triazoles and *Candida* species are concerned, there are disconcerting reports that indicate that some yeasts may have either developed or are developing resistance (Evans *et al.*, 1991; Smith *et al.*, 1991a; Johnson *et al.*, 1993).

The development of cross-resistance of *C. albicans* to different imidazoles during treatment with a single azole derivative has been described (Holt and Azmi, 1978; Johnson *et al.*, 1984).

C. DNA Analogues

1. Flucytosine (5-Fluorocytosine)

This DNA analogue, which interferes with nucleic acid synthesis of the yeast cells, may be useful as oral therapy for systemic fungal infections in a dose of 50 to 150 mg/kg/d in divided doses four times daily. Toxicity is due to metabolic effects on rapidly dividing host cells such as bone marrow cells. Other side effects are nausea, vomiting, and hepatic dysfunction (Epstein, 1990).

XIII. CONCLUDING REMARKS

Although considerable progress has been made in the understanding of *Candida* and oral candidosis during the last few decades, much remains to be done. The precise nature of determinants of virulence of *Candida*, and the response of host tissues to them, are still unclear, although our knowledge on these and other aspects of *Candida* pathogenicity has advanced considerably due to recent applications of molecular biological techniques to investigate phenomena such

as phenotypic switching. The increasing prevalence of oral *Candida* infections in HIV-infected patients and the emergence of antifungal resistance to the newer azoles has in addition renewed the vigor and impetus of *Candida* research. Because of a combination of recent knowledge and increasingly sophisticated technology, the future for *Candida* research will doubtless be fruitful, exciting, and highly rewarding.

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